



PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Frederic Becq et al.	Confirmation No.:	4276
Serial No.:	10/516,839	Art Unit:	1625
Filed:	March 4, 2005	Examiner:	Charanjit Aulakh
Customer No.:	21559		
Title:	Use of Benzo[c]Quinolizinium Derivatives for the Treatment of Diseases that are Linked to Smooth Muscle Cell Constriction		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF DR. FRÉDÉRIC BECQ UNDER 37 C.F.R. § 1.132
TRAVERSING GROUNDS OF REJECTION

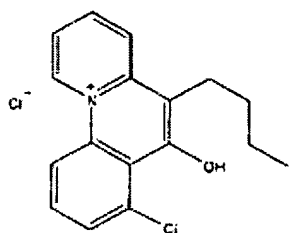
Under 37 C.F.R. § 1.132 and regarding the rejection of claims 23-30 for lack of enablement, I declare:

1. I am an inventor of the subject matter that is described and claimed in the above-captioned patent application. I hold the degree of Ph.D.
2. I am a Professor of Physiology at the Université de Poitiers and Director of the

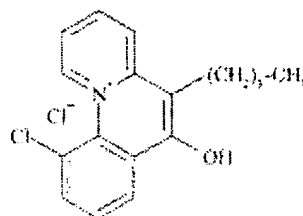
Joint Unit of Research for the Institute of Cellular Physiology and Biology at the National Center for Scientific Research (CNRS).

3. I have read and understood the Office Action mailed on October 29, 2008, in connection with the above-referenced patent application and I understand that claims 23-30 are rejected as lacking enablement for the treatment of bronchoconstriction.

4. In support of the enablement of claims 23-30, I am providing data showing that two benzo[c]quinolizinium compounds of formula (Ia) can relax bronchi as described in the pending application. The structures of these two compounds, MPB-104 and MPB-91, are provided below.



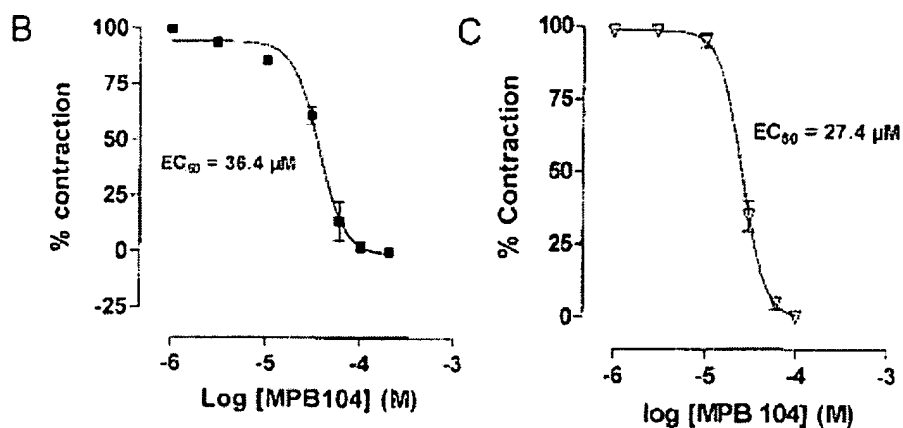
MPB-104



MPB-91

5. In vitro contraction measurements were made on isolated tracheal rings mounted between a fixed clamp at the base of a water-jacketed organ bath. Carbachol was used to evoke a sustained contractile response. Once the sustained tension was established, the test compound was added to the bath. The cumulative concentration-

response relationship for the test compound was measured in the trachea rings following stable contraction. The relaxant effect of the compound is expressed as percentage contraction of the tracheal rings (see plotted data below: curve B is data for MPB-104



on human trachea, curve C is data for MPB-104 on rat trachea).

6. The activity of a compound is expressed as an EC_{50} , which is calculated as the drug concentration inducing a half-maximal dilatation. MPB-104 was found to have an EC_{50} of $36.4 \mu M$ on human trachea and an EC_{50} of $27.4 \mu M$ on rat trachea. MPB-91 was found to have an EC_{50} of $12 \mu M$ on human trachea. These results show that benzo[c]quinolizinium compounds can relax constricted bronchi and can be useful for the treatment of conditions associated with bronchoconstriction, such as asthma.

7. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Date 30 03 2009

Frédéric Becq, Ph.D.

A large, stylized handwritten signature in black ink, consisting of several overlapping loops and a long horizontal stroke, is written over the printed name and extends to the right.